Please amend Claims 8, 9, 10, and 13 to read as follows:

8. (Amended) The process according to Claim 6 wherein said template is of human origin.

9. (Amended) The process according to Claim 7 wherein said template is of human origin.

10. (Amended) An isolated polynucleotide comprising a contiguous stretch of at least about 30 nucleotides of at least one of SEQ ID NO:9, 13, 14, 17, or 18.

13. (Amended) An isolated polynucleotide of at least about 40 nucleotides capable of hybridizing to a polynucleotide consisting of a sequence selected from the group consisting of SEQ ID NO:9, 12, 13, 14, 16, 17, and 18, under high stringency conditions, said conditions comprising incubating at 65°C in 0.5M $NaHP0_4$, 7% sodium dodecyl sulfate (SDS), 1mM EDTA and washing at 68°C in 0.1xSSC and 0.1% SDS.

REMARKS

Claims 3 and 5-13 are pending in the instant application. Applicants submit that Claims 8, 9, 10, and 13 have been amended to particular point out and distinctly claim the subject matter which the inventors regard as the invention. Specifically, claims 8 and 9 have been amended to correct Examiner's objection as to informalities. Claims 8 and 9 have been amended to recite "said template is" in each claim. Claim 13 has been amended to recite specific hybridization conditions. The amendments are fully supported by the specification and claims as originally filed, they do not constitute new matter. The amended claims are supported in the specification, *inter alia*, at page 13, line 1 to page 14 lines 2.

I. THE INVENTION

The present invention relates, in part, to polynucleotides that are discovered using gene trap technology. The gene trap vectors used in the invention can integrate into intron sequences of cellular genes. The cellular genes in which the vector are inserted (the "trapped genes") may be cloned easily since the vectors are designed such that fusion transcripts are formed with the trapped genes. The fusion transcripts comprise exon

sequences of the trapped gene appended to a selectable marker that facilitates isolation by polymerase chain reaction-based protocols or by cDNA cloning. In some cases, integration disrupts the transcription of the trapped gene and results in a null mutation at the locus. In this application, the claimed invention relates to polynucleotides comprising the disclosed polynucleotide sequences of SEQ ID NOS:9-18 which are trapped genes obtained from human teratocarcinoma cells. The present invention also relates to an *in vitro* process for producing a polynucleotide that encodes nucleotides in SEQ ID NOS:9, 10, 12-14, 16-18.

II. THE REJECTION UNDER 35 U.S.C. § 101 IS IN ERROR

Claims 3, and 5-13 are rejected by the Examiner under 35 U.S.C. § 101 as allegedly lacking patentable utility for the lack of a specific, substantial, and credible utility. Claims 3, and 10-13 recite polynucleotides comprising the disclosed polynucleotide sequences of SEQ ID NOS:9-18. Claims 5-9 recite an *in vitro* process for producing a polynucleotide that encodes polynucleotides sequences of SEQ ID NOS:9, 10, 12-14, 16-18. The Examiner stated that a method of making a compound or composition which does not have utility also does not have utility. Applicants respectfully traverse the rejection on the ground that such polynucleotides have specific, substantial, and credible utility and hence a process for producing a polynucleotide also have specific, substantial, and credible utilities as described in the specification.

The Examiner stated that a nucleic acid that simply used as markers to detect diseases, biological events, cell types, and tissues, do not constitute a specific utility because the specification fails to disclose a nexus between any, or all, of the claimed nucleic acid sequences and any particular disease, biological event, or cell or tissue type. The Examiner further asserted that:

> Some uses, such as diagnostic gene expression assays, genomic and chromosome mapping, and identification of diseases, biological events, tissues, etc. are utilities which apply to a subset of all nucleic acid sequences. . . . There is no evidence that this is necessarily the case, however, and the uses set forth above are still those which apply to a wide variety of nucleic acid sequences.

According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular practical purpose (*i.e.*, it has a "specific and substantial utility") and the assertion would be considered credible

by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 FR1098 January 5, 2001). A description of specific utility may be found in the Revised Interim Utility Guidelines Training Materials. Specific utility is:

> "a utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed." (http://www.uspto.gov/web/menu/utility).

Unlike the example cited in the above definition where any fragment of genomic DNA can in theory be used as a probe or a chromosome marker, the polynucleotide sequences of SEQ ID NOS:9-18 has specific utility.

According to the invention, gene trap vectors were introduced into human teratocarcinoma cells which result in the identification of the gene loci that comprise the sequences set forth in SEQ ID NOS: 9-18. After the gene trap vector had integrated nonspecifically into the human teratocarcinoma cell genome, fusion transcripts were expressed. Each fusion transcript comprises exons that are located either upstream or downstream from the integration site. These exons, which are portions of a genetic locus that was disrupted by a gene trap vector, were cloned and represented by the presently claimed polynucleotides.

The genetic loci, as represented by the presently claimed polynucleotides, which have been disrupted in the teratocarcinoma cells fall within a specific class of genes which are distinct from the broad general class of genes in the genome. Applicants point out that there is a nexus between all of the claimed nucleic acid sequences and a particular type of biological event associated with a type of cells. These genetic loci encode genetic functions which are not involved in the general survival, *i.e.* house-keeping functions, of teratocarcinoma cells and that both copies of functional allele at these loci are not required for survival. The teratocarcinoma cells, after transfection with the gene trap vectors, survived and propagated with only one non-disrupted allele of the genetic loci. These genetic loci and the products encoded by these loci are essentially preselected by the transfection for

possessing functions that are specifically involved in the differentiation and development of such cells.

Applicants submit that the present invention can be used to identify and study genes that are involved in the late stages of stem cell differentiation and development. This is due to the unique nature of teratocarcinoma cells which are "stem cells" that occur in unusual germ cell tumors. Stem cells are defined by the ability both to produce identical daughter cells (self-renewal), and to produce progeny with more restricted fates (commitment and differentiation). This property of stem cells underpins growth and diversification during development and sustains homeostasis and repair processes throughout adult life. An understanding of molecular mechanisms which govern stem cell fate is therefore of fundamental significance in cell and developmental biology and the capabilities arising from such knowledge have major biomedical applications.

In many ways, teratocarcinoma cells resemble normal embryonic stem cells and represent a good model for molecular mechanisms of embryonic development and differentiation. Applicants submit that genes that are critically essential to the survival of teratocarcinoma cells would not have been isolated and propagated by the gene trap methods of the invention, and would likely have been eliminated after the transfection with gene trap vectors. Thus, the sequences set forth in SEQ ID NOS: 9-18 represent a sample of genetic sequences that may play a role in late stages of stem cell differentiation and development. Accordingly, the utility of these sequences are not general and are not shared by any random pieces of genomic DNA. Not every gene in the genome necessarily provide this specific utility of the polynucleotides of the invention. Applicants submit that these genetic loci as represented by the presently claimed polynucleotides have substantial utility because they provide useful information regarding gene expression in teratocarcinoma cells which mimics gene expression during the late stages of stem cell differentiation and development.

Applicants submit that the claimed polynucleotides can be used as probes in hybridization assays well known in the art to determine the activity at the genetic loci during development and differentiation of the teratocarcinomas (See for example, page 39, line 7 to page 42, line 20). Teratocarcinomas are totipotent which means that they may be differentiated into many different cell types (such as teeth, hair, bone, muscle and cartilage) along various pathways upon induction by certain signals. Each of these pathways may require expression of one or more genes that are disclosed in the specification as filed and

represented by the presently claimed polynucleotides. Thus, the claimed polynucleotides can be used as probes, for example, in Northern blot analysis (page 41, lines 3-8), or in situ hybridization (page 41, lines 8-11), for undifferentiated teratocarcinomas or differentiated teratocarcinomas of different lineages or at different stages of differentiation and development. The expression pattern of each of these genes can thus be correlated with known events that occur in particular stages of development and cell differentiation. As such, the utility is substantial and credible in a real world context.

The above described techniques are well known in the art and hence utilities of the present invention are credible. As stated in the Examination Guidelines for the Utility Requirement, credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure or any other evidence of record. Furthermore, the Revised Interim Utility Guidelines Training Materials states that assertion of utility is credible if it is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided. Accordingly, not only do the polynucleotides of the present invention have specific utilities, their utilities are credible and practical.

Since the polynucleotides of the present invention as described in claims 3, and 10-13 have specific, substantial and credible utility, a method of making the claimed polynucleotides which have utility, as described in claims 5-9, also have utility.

In view of the foregoing, Applicants submit that the claimed invention has specific, substantial and credible utility. Thus, Applicants respectfully request that the rejection of claims 3, and 5-13 under 35 U.S.C. § 101 be withdrawn.

III. THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH SHOULD BE WITHDRAWN

Claims 3, and 5-13 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking utility. Applicants traverse this rejection on the ground that Claims 3, and 5-13 have significant patentable utility as discussed in Section II, above. Applicants submit that when an Applicant satisfactorily rebuts a rejection based on a lack of utility under 35 U.S.C. § 101, the corresponding rejection imposed under 35 U.S.C. § 112, first paragraph, should also be withdrawn. Thus, Applicants respectfully request that the rejection of Claims 3, and 5-13 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claims 3, and 10-13 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification. The Examiner states:

> With the exception of the specific sequences corresponding to SEQ ID NO's 9-18, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation.

Applicants traverse this rejection. Claims 3, and 10-13 indeed are fully supported by the specification and claims as originally filed.

35 U.S.C. § 112, first paragraph, requires that the specification contain a written description of the invention. An applicant must convey with reasonable clarity to those skilled in the art that the applicant was in possession of the invention. Vas-Cath v. Mahurkar, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). "The written description must communicate that which is needed to enable the skilled artisan to make and use the claimed invention." Kennecott Corp. v. Kyocera Int'l, Inc., 835 F.2d 1419, 1421, 5 U.S.P.Q.2d 1194, 1197 (Fed. Cir. 1987), cert. denied, 486 U.S. 1008 (1988).

Moreover, according to the Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶ 1, "Written Description" Requirement (Federal Register v. 66, no. 4, pages 1099-1111, January 5, 2001, the "Guidelines"), the written description requirement may be satisfied by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

Claims 3, and 10-13 recite isolated polynucleotides corresponding to one of SEQ ID NOS:9-18. The isolated polynucleotides are fully described by *structure* or by *physical properties*, or both, sufficient to distinguish the claimed isolated polynucleotides from other materials. For instance, Claim 3 recites isolated polynucleotide that comprise a contiguous stretch of at least about 60 nucleotides of at least one of SEQ ID NOS:9, 12-14, 16-18. As the exact structure of SEQ ID NOS:9, 12-14, and 16-18 are provided in the specification, although there are numerous polynucleotides that falls within this description, one person of skilled in the art can make the synthetic oligonucleotide as described in claim

3. Likewise, claim 13 has been amended to describe a genus of polynucleotides by a property (i.e., hybridizable under defined conditions to known sequences) that readily distinguishes the claimed polynucleotides from other materials. One of skill in the art can readily isolate the claimed polynucleotides of claim 13 and distinguish it from other polynucleotides by performing a hybridization as recited in the claim.

Applicants respectfully point out that the chemical structure of the claimed genus of nucleic acid molecules are described and well known in the art (e.g., DNA, RNA) and that the variation of nucleotide sequence within the claimed genus is also well defined by the functional characteristics of specifically binding under defined hybridizing conditions to nucleic acid molecules of known sequences. See footnote 42 of the Guidelines wherein it is stated that examples of identifying characteristics include a sequence, structure, binding affinity, binding specificity, molecular weight, and length, and also detailed restriction enzyme maps, antibody cross-reactivity, unique cleavage by particular enzymes. One of skill in the art would recognize from the combination of identifying structural and functional characteristics disclosed in the specification that Applicants have possession of the claimed genus of nucleic acid molecules. In fact, the skilled person can readily recognize and determine whether a nucleic acid molecule falls within the pending claims by either comparing the sequence of the molecule with the sequences provided in the application and/or performing a hybridization reaction under defined conditions with the nucleic acid molecule(s) described in the present application. As such, Applicants submit that adequate written description has been provided.

The Examiner stated that only polynucleotide sequences consisting of SEQ ID NO's 9-18, but not the full breadth of the claims, meets the written description requirement. The Examiner asserted that the species specifically disclosed are not representative of the genus because the genus is highly variant. Applicants submit that the specification discloses exemplary elements that may be included in the claimed polynucleotides, such as non-coding or regulatory regions (page 23, lines 7-24); vector sequences (page 23, lines 7-17), other coding sequences as obtained by "primer extension" (page 10, lines 21-27). As such, the specification is replete with description of representative elements that may be included in the claimed polynucleotides. Applicants submit that the written description requirement for the claimed genus of molecules are met.

In view of the foregoing, Applicants respectfully request that the rejection of Claims 3, and 10-13 under 35 U.S.C. § 112, first paragraph, be withdrawn.

IV. THE REJECTIONS UNDER 35 U.S.C. § 102(b) SHOULD BE WITHDRAWN

Claim 10 stands rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by EST Accession No. AQ416115 ("Zhao AQ416115") by Hoof et al., 1992, Nucleic Acids Res. 20:5475 ("Hoof"); by Chu et al., 1993, Nucleic Acids Res. 21:1672 ("Chu"); by Saha et al., 1993, Gene 132:285-289 ("Saha"). The Examiner asserts that Hoof, Chu or Saha, each teaches an oligonucleotide comprising a contiguous stretch of 29 bases of SEQ ID NO:16. Applicants have amended claim 10 to recite an isolated polynucleotide that comprises at least about 30 nucleotides of SEQ ID NOS:9, 13, 14, 17, or 18. As such, claim 10 no longer recites SEQ ID NO:16.

Since Hoof, Chu, Saha, alone or in any combination, do not teach or suggest each and every element of amended claim 10, these references do not anticipate claim 10. Applicants request that the rejections of claim 10 under 35 U.S.C. § 102(b) be withdrawn.

CONCLUSION

Applicants submit that Claims 3, and 5-13 satisfy all of the criteria for patentability and are in condition for allowance. An early indication of the same and passage of Claims 3, and 5-13 to issuance is therefore kindly solicited.

If any issues remain, it is requested that the undersigned be contacted by telephone to discuss same.

Respectfully submitted,

Date: January 17, 2002

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Exhibit A
Marked-Up Version of Amended Claims

8. (Amended) The process according to Claim 6 wherein said [templates are] template is of human origin.

9.(Amended) The process according to Claim 7 wherein said [templates are] template is of human origin.

10. (Amended) An isolated polynucleotide comprising a contiguous stretch of at least about 30 nucleotides of at least one of SEQ ID NO:9, 13, 14, [16-18] 17, or 18.

13. (Amended) An isolated polynucleotide of at least about 40 nucleotides capable of hybridizing to a polynucleotide [of Claim 3, 10 or 11] consisting of a sequence selected from the group consisting of SEQ ID NO:9, 12, 13, 14, 16, 17, and 18, under high stringency conditions, said conditions comprising incubating at 65°C in 0.5M $NaHP0_4$, 7% sodium dodecyl sulfate (SDS), 1mM EDTA and washing at 68°C in 0.1xSSC and 0.1% SDS.

Exhibit B
Pending Claims

3. An isolated polynucleotide comprising a contiguous stretch of at least about 60 nucleotides of at least one of SEQ ID NOS:9, 12-14, 16-18.

5. An *in vitro* process for producing a polynucleotide comprising the steps of:

a) obtaining a polynucleotide template encoding a sequence capable of hybridizing to a gene trapped sequence of SEQ ID NOS:9, 10, 12-14, 16-18;

b) combining said template with a synthetic oligonucleotide sequence of about 14 to about 80 bases in length that comprises a contiguous sequence of at least about 12 nucleotides disclosed in one of SEQ ID NOS:9, 10, 12-14, 16-18; and

c) processing the combined oligonucleotide and template preparation such that said oligonucleotide sequence hybridizes to said template in the presence of a DNA polymerase molecule and a sufficient concentration of dNTPs for said oligonucleotide sequence to prime DNA synthesis by said polymerase,

wherein a polynucleotide is produced that encodes at least about 50 contiguous nucleotides first disclosed in one of SEQ ID NOS:9, 10, 12-14, 16-18.

6. The process of Claim 5 wherein said template is mammalian cDNA.

7. The process of Claim 5 wherein said template is mammalian genomic DNA.

8. The process according to Claim 6 wherein said template is of human origin.

9. The process according to Claim 7 wherein said template is of human origin.

10. An isolated polynucleotide comprising a contiguous stretch of at least about 30 nucleotides of at least one of SEQ ID NO:9, 13, 14, 17, or 18.

11. An isolated polynucleotide comprising a contiguous stretch of at least about 40 nucleotides of at least one of SEQ ID NO:9, 12-14, 16-18.

12. An isolated polynucleotide comprising at least one of SEQ ID NOS:9-18.

13. An isolated polynucleotide of at least about 40 nucleotides capable of hybridizing to a polynucleotide consisting of a sequence selected from the group consisting of SEQ ID NO:9, 12, 13, 14, 16, 17, and 18, under high stringency conditions, said conditions comprising incubating at 65°C in 0.5M $NaHP0_4$, 7% sodium dodecyl sulfate (SDS), 1mM EDTA and washing at 68°C in 0.1xSSC and 0.1% SDS.